WEST

Generate Collection Print

L6: Entry 4 of 12 File: USPT Jul 31, 2001

US-PAT-NO: 6268533
DOCUMENT-IDENTIFIER: US 6268533 B1

TITLE: Formoterol process

DATE-ISSUED: July 31, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Gao; Yun	Southborough	MA		
Hett; Robert	Aarau			CH
Fang; Kevin Q.	Wellesley	MA		
Wald; Stephen A.	Sudbury	MA		
Senanayake; Chris Hugh	Shrewsbury	MA		

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Sepracor Inc.	Marlborough	MA			02

APPL-NO: 09/ 493042 [PALM]
DATE FILED: January 27, 2000

PARENT-CASE:
CROSS REFERENCE TO RELATED APPLICATIONS This application is a divisional of prior application Ser. No. 09/083,010, filed May 21, 1998, now U.S. Pat. No. 6,040,344, which was a continuation-in-part of application Ser. No. 08/747,592, filed Nov. 12, 1996, now abandoned, the entire disclosures of which are incorporated herein by reference.

INT-CL: [07] C07 C 217/52

US-CL-ISSUED: 564/216; 549/520, 549/553, 564/220, 564/221, 564/389, 564/417, 564/447, 568/586
US-CL-CURRENT: 564/216; 549/520, 549/553, 564/220, 564/221, 564/389, 564/417, 564/447, 568/586

FIELD-OF-SEARCH: 564/216, 564/220, 564/221, 564/389, 564/417, 564/442, 568/586, 549/520, 549/553

PRIOR-ART-DISCLOSED:

FOREIGN REFS GROUP (TEST)

390762 19901000 EP
2005492 19890300 ES
2031407 19921200 ES
WO92/05147 19920400 WO

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
390762	October 1990	EP	
2005492	March 1989	ES	
2031407	December 1992	ES	
WO92/05147	April 1992	WO	

OTHER PUBLICATIONS

Hett et al. "Large Scale Synthesis of Enantio- and Diastereomerically Pure (R,R)-Formoterol" Organic Proc. Res. & Dev. 2, 96-99 (1998).
Hett et al. "Conformational Toolbox of Oxazaborolidine Catalysts in the Enantioselective . . . " Tet. Lett. 39, 1705-1708 (1998).
Hett et al. "Enantio- and Diastereoselective Synthesis of all Four Stereoisomers of Formoterol" Tet. Lett. 38, 1125-1128 (1997).
Murase et al. "New .beta.-Adrenoreceptor Stimulants. Studies on 3-Acylamino-4-hydroxy- . . . " Chem. Pharm. Bull. 25(6), 1368-1377 (1977).
Murase et al. "Absolute Configurations of Four Isomers of 3--Formamido--4 --hydroxy--. . . " Chem. Pharm. Bull. 26(4), 1123-1129 (1978).
Trofast et al. "Steric Aspects of Agonism and Antagonism at .beta.-Adrenoceptors: Synthesis . . . " Chirality 3, 443-450 (1991).
Kurihara et al. "(-)+-Formoterol, .dagger. a Selective .beta..sub.2 --Adrenoreceptor Agonist" Acta Cryst. C53, 1887-1889 (1997).

ART-UNIT: 164

PRIMARY-EXAMINER: Raymond; Richard L.

ABSTRACT:

A method is disclosed for the preparation of optically pure isomers of formoterol by the reaction of an optically pure 4-benzyloxy-3-formamidostyrene oxide with an optically pure 4-methoxy-.alpha.-methyl-N-(phenylmethyl)benzeneethanamine followed by debenzylation. Useful intermediates in the process are also disclosed, as are the novel L-tartrate salt of R,R-formoterol and pharmaceutical compositions thereof.

20 Claims, 0 Drawing figures


WEST

Help | Logout | Interrupt

Main Menu | Search Form | Posting Counts | Show S Numbers | Edit S Numbers | Preferences | Cases

Search Results -

Terms	Documents
L2 isomer near3 formoterol	12

Database: US Patents Full-Text Database; US Pre-Grant Publication Full-Text Database; JPO Abstracts Database; EPO Abstracts Database; Derwent World Patents Index; IBM Technical Disclosure Bulletins

Search: L6

Refine Search | Recall Text | Clear

Search History

DATE: Monday, August 19, 2002 Printable Copy Create Case

Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT,PGPB,JPAB,EPAB,DWPI; PLUR=YES; OP=AND			
L6	L2 isomer near3 formoterol	12	L6
L5	L2 isomer	60	L5
L4	L2 racemate	28	L4
L3	L2 (R,R)-formoterol	23	L3
L2	L1 (inhalation or inhaler)	260	L2
L1	formoterol	408	L1

END OF SEARCH HISTORY

PDR® entry for

FORADIL® AEROLIZER™ (Novartis)
(formoterol fumarate inhalation powder)

FOR ORAL INHALATION ONLY
Rx only

Description

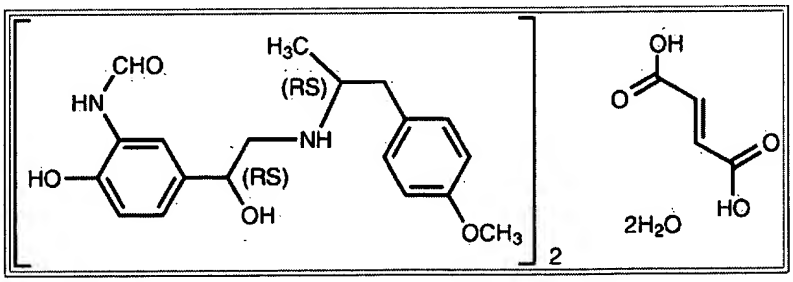
The following prescribing information is based on official labeling in effect July 2001.

DESCRIPTION

FORADIL® AEROLIZER™ consists of a capsule dosage form containing a dry powder formulation of Foradil (formoterol fumarate) intended for oral inhalation only with the Aerolizer™ Inhaler.

Each clear, hard gelatin capsule contains a dry powder blend of 12 mcg of formoterol fumarate and 25 mg of lactose as a carrier.

The active component of Foradil is formoterol fumarate, a racemate. Formoterol fumarate is a selective beta $_2$ -adrenergic bronchodilator. Its chemical name is (±)-2-hydroxy-5-[(1RS)-1-hydroxy-2-[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]- amino]ethyl]formanilide fumarate dihydrate; its structural formula is



Formoterol fumarate has a molecular weight of 840.9, and its empirical formula is $(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4 \cdot 2H_2O$. Formoterol fumarate is a white to yellowish crystalline powder, which is freely soluble in glacial acetic acid, soluble in methanol, sparingly soluble in ethanol and isopropanol, slightly soluble in water, and practically insoluble in acetone, ethyl acetate, and diethyl ether.

The Aerolizer Inhaler is a plastic device used for inhaling Foradil. The amount of drug delivered to the lung will depend on patient factors, such as inspiratory flow rate and inspiratory time. Under standardized

in vitro testing at a fixed flow rate of 60 L/min for 2 seconds, the Aerolizer Inhaler delivered 10 mcg of formoterol fumarate from the mouthpiece. Peak inspiratory flow rates (PIFR) achievable through the Aerolizer Inhaler were evaluated in 33 adult and adolescent patients and 32 pediatric patients with mild-to-moderate asthma. Mean PIFR was 117.82 L/min (range 34-188 L/min) for adult and adolescent patients, and 99.66 L/min (range 43-187 L/min) for pediatric patients. Approximately ninety percent of each population studied generated a PIFR through the device exceeding 60 L/min.

To use the delivery system, a Foradil capsule is placed in the well of the Aerolizer Inhaler, and the capsule is pierced by pressing and releasing the buttons on the side of the device. The formoterol fumarate formulation is dispersed into the air stream when the patient inhales rapidly and deeply through the mouthpiece.

(*back to top*)

CLINICAL PHARMACOLOGY

Mechanism of Action

Formoterol fumarate is a long-acting selective beta $_2$ -adrenergic receptor agonist (beta $_2$ -agonist). Inhaled formoterol fumarate acts locally in the lung as a bronchodilator. In vitro studies have shown that formoterol has more than 200-fold greater agonist activity at beta $_2$ -receptors than at beta $_1$ -receptors. Although beta $_2$ -receptors are the predominant adrenergic receptors in bronchial smooth muscle and beta $_1$ -receptors are the predominant receptors in the heart, there are also beta $_2$ -receptors in the human heart comprising 10%-50% of the total beta-adrenergic receptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective beta $_2$ -agonists may have some effect on the cardiovascular system.

The pharmacologic effects of beta $_2$ -adrenoceptor agonist drugs, including formoterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

In vitro tests show that formoterol is an inhibitor of the release of mast cell mediators, such as histamine and leukotrienes, from the human lung. Formoterol also inhibits histamine-induced plasma albumin extravasation in anesthetized guinea pigs and inhibits allergen-induced eosinophil influx in dogs with airway hyper-responsiveness. The relevance of these in vitro and animal findings to humans is unknown.

Animal Pharmacology

Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently. The clinical significance of these findings is unknown.

Pharmacokinetics

Information on the pharmacokinetics of formoterol in plasma has been obtained by oral inhalation of doses higher than the recommended range. Urinary excretion of unchanged formoterol was used as an indirect measure of systemic exposure. Plasma drug disposition data parallel urinary excretion, and the elimination

half-lives calculated for urine and plasma are similar.

Absorption

Following inhalation of a single 120 mcg dose of formoterol fumarate by 12 healthy subjects, formoterol was rapidly absorbed into plasma, reaching a maximum drug concentration of 92 pg/mL within 5 minutes of dosing.

Following inhalation of 12 to 96 mcg of formoterol fumarate by 10 healthy males, urinary excretion of both (R,R)- and (S,S)-enantiomers of formoterol increased proportionally to the dose. Thus, absorption of formoterol following inhalation appeared linear over the dose range studied.

In a study in patients with asthma, when formoterol 12 or 24 mcg twice daily was given by oral inhalation to steady-state, the accumulation index ranged from 1.67 to 2.08, based on the urinary excretion of unchanged formoterol. This suggests some accumulation of formoterol in plasma with multiple dosing. The excreted amounts of formoterol at steady-state were close to those predicted based on single-dose kinetics.

As with many drug products for oral inhalation, it is likely that the majority of the inhaled formoterol fumarate delivered is swallowed and then absorbed from the gastrointestinal tract.

Distribution

The binding of formoterol to human plasma proteins in vitro was 61%-64% at concentrations from 0.1 to 100 ng/mL. Binding to human serum albumin in vitro was 31%-38% over a range of 5 to 500 ng/mL. The concentrations of formoterol used to assess the plasma protein binding were higher than those achieved in plasma following inhalation of a single 120 mcg dose.

Metabolism

Formoterol is metabolized primarily by direct glucuronidation at either the phenolic or aliphatic hydroxyl group and O-demethylation followed by glucuronide conjugation at either phenolic hydroxyl groups. The most prominent pathway involves direct conjugation at the phenolic hydroxyl group. The second major pathway involves O-demethylation followed by conjugation at the phenolic 2'-hydroxyl group. Four cytochrome P450 isozymes (CYP2D6, CYP2C19, CYP2C9 and CYP2A6) are involved in the O-demethylation of formoterol. Formoterol did not inhibit CYP450 enzymes at therapeutically relevant concentrations.

Excretion

Following oral administration of 80 mcg of radiolabeled formoterol fumarate to 2 healthy subjects, 59%-62% of the radioactivity was eliminated in the urine and 32%-34% in the feces over a period of 104 hours. Renal clearance of formoterol from blood in these subjects was about 150 mL/min. Following inhalation of a 12 mcg or 24 mcg dose by 16 patients with asthma, about 10% and 15%-18% of the total dose was excreted in the urine as unchanged formoterol and direct glucuronide conjugates of formoterol, respectively.

Based on plasma concentrations measured following inhalation of a single 120 mcg dose by 12 healthy subjects, the mean terminal elimination half-life was determined to be 10 hours. From urinary excretion rates measured in these subjects, the mean terminal elimination half-lives for the (R,R)- and